IL-2 immunotherapy fails to benefit HIV-infected individuals already taking antiretrovirals

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Providing a synthetic form of the immune system protein interleukin-2 (IL-2) to HIV-infected individuals already taking combination antiretroviral therapy boosts their numbers of CD4+ T cells, the key white blood cells destroyed by HIV, but fails to reduce their risk of HIV-associated opportunistic diseases or death compared with combination antiretroviral therapy alone.

These are the findings of two large international clinical trials presented today at the Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal.

The Phase III trials, known as the ESPRIT and SILCAAT studies, were sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and funded respectively by NIAID and Chiron Corp. of Emeryville, Calif. (since 2006 part of Novartis Pharmaceuticals).

Marcelo H. Losso, M.D., of Hospital José María Ramos Mejía, Buenos Aires, Argentina, presented the results of ESPRIT, and Yves Levy, M.D., of Hôpital Henri Mondor, Créteil, France, presented the results of SILCAAT.

IL-2 is produced naturally in the body and plays an important role in regulating CD4+ T cell production and survival. As their CD4+ T cell

levels drop, people infected with HIV become more vulnerable to AIDS-related opportunistic diseases and death. Earlier research established that giving synthetic IL-2 plus antiretroviral therapy to people with HIV infection boosts their CD4+ T cell counts more than does antiretroviral therapy alone, but it was unknown whether this boost translated into better health. ESPRIT and SILCAAT were designed to test whether giving IL-2 to HIV-infected individuals already on antiretroviral therapy would keep them healthier longer than HIV-infected individuals taking only antiretrovirals.

Together, the ESPRIT and SILCAAT studies involved more than 5,800 HIV-infected volunteers in 25 countries. Participants were assigned at random to receive either combination antiretroviral therapy alone or combination antiretrovirals plus injections of Proleukin (Novartis Pharmaceuticals, Basel, Switzerland), a synthetic form of IL-2, over several five-day cycles. To evaluate the effects of IL-2 treatment at different stages of HIV infection, the ESPRIT study enrolled people with early-stage infection (CD4+ T cell counts at or above 300 cells per cubic millimeter, or mm3), while the SILCAAT study enrolled volunteers with later-stage HIV infection (CD4+ T cell counts between 50 and 299 cells/ mm3).

"In both studies, the volunteers who received IL-2 and antiretrovirals experienced notable, sustained increases in CD4+ T cell counts, as anticipated," notes NIAID Director Anthony S. Fauci, M.D. "Unfortunately, these increases did not translate into reduced risks of HIV-associated opportunistic diseases or death when compared with the risks in volunteers who were taking only antiretrovirals. Although further analyses may help us better understand these findings, the two studies clearly demonstrated that the use of IL-2 did not improve health outcomes for HIV-infected people."

It is unclear why increased CD4+ T cell counts did not translate into

better health outcomes. James D. Neaton, Ph.D., of the University of Minnesota, principal investigator of the global clinical trials network that conducted ESPRIT, offers two possible explanations. "It could be that the types of CD4+ T cells induced by IL-2 play no role in protecting the HIV-infected patient, and therefore the administration of IL-2 has no benefit," says Dr. Neaton. "A second possibility is that the CD4+ T cells are at least somewhat functional or that IL-2 has some modest benefit, but that the side effects of IL-2 may neutralize any possible benefit."

"In the end, the results of these two studies indicate that although a person's number of CD4+ T cells is a key measure of success in the treatment of HIV with antiretroviral drugs, we can't rely on CD4+ T cell counts to predict whether immune-based therapies such as IL-2 will improve the health of HIV-infected individuals," concludes Dr. Levy, the principal investigator of SILCAAT.

"The purpose of clinical research is to clearly state and accurately test hypotheses with an ultimate goal of improving patient care," notes H. Clifford Lane, M.D., director of clinical research at NIAID and a member of the executive committee of ESPRIT. "These two clinical trials successfully reached a definitive answer about the utility of IL-2 therapy for treating HIV infection. NIAID thanks the thousands of dedicated volunteers and investigators who made these studies possible. The results will have significant implications for the future development of immune-based therapies for HIV and studies of HIV pathogenesis."

Background Information on ESPRIT and SILCAAT

The ESPRIT study—which stands for "Evaluation of Subcutaneous Proleukin in a Randomized International Trial"—began in March 2000 and ended as scheduled in November 2008. It was coordinated by the international centers of the NIAID-sponsored International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). These centers are

the Medical Research Council Clinical Trials Unit in London; the Copenhagen HIV Program in Denmark; the National Centre in HIV Epidemiology and Clinical Research at the University of New South Wales in Sydney, Australia; and the Community Programs for Clinical Research on AIDS (CPCRA) unit in Washington, D.C. The study's statistical and data management center was based at the University of Minnesota in Minneapolis.

The study investigators followed 4,111 HIV-infected men and women ages 18 and older in 25 countries at 252 clinical trial sites. Half of the volunteers were injected with 7.5 million international units (MIUs) of Proleukin twice a day for five consecutive days every eight weeks for at least six months. After six months, volunteers could receive additional IL-2 cycles at the discretion of their physicians to maintain CD4+ T cell counts at twice their baseline levels or greater than 1,000 cells/mm3 for as long as possible. All volunteers were assessed every four months for an average of seven years to monitor CD4+ T cell counts, viral load (the amount of HIV in the blood) and signs of illness.

In analyzing the ESPRIT results, researchers found that although volunteers who received IL-2 maintained a higher CD4+ T cell count (an average of 160 cells/mm3 higher) than those in the antiretroviral-only study group, there was no difference in the rate of HIV-associated opportunistic diseases or death between the two groups.

The SILCAAT study—short for "Subcutaneous, Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active Antiretroviral Therapy"—began in April 1999, ended in November 2008, and was conducted by the same international coordinating center structure that conducted ESPRIT. While SILCAAT was funded primarily by Chiron Corp., sponsorship of SILCAAT shifted from the Chiron Corp. to NIAID's Division of Clinical Research in 2003. The study investigators followed 1,695 HIV-infected adults in 11

countries at 114 clinical trial sites. Volunteers assigned to the IL-2 group received 4.5 MIUs of Proleukin twice a day for five consecutive days every eight weeks for one year. After that point, participants could receive additional IL-2 cycles to maintain their CD4+ T cell counts at 125 to 175 cells/mm3 above baseline. All volunteers were assessed every four months for approximately seven years.

As in the ESPRIT study, the SILCAAT volunteers who received IL-2 experienced a higher CD4+ T cell count (an average of 59 cells/mm3 higher) than those who received only antiretrovirals, but there was no difference in health outcomes between the two groups.

Additionally, IL-2 recipients in both studies experienced a greater number of serious clinical events already known to be associated with IL-2, including disorders of the heart and blood vessels, injection site reactions and such psychiatric disorders as depression and suicidal behavior.

Participants in the ESPRIT and SILCAAT clinical trials were promptly informed of the findings. Additionally, NIAID has discontinued the use of IL-2 in a separate, 20-country clinical trial known as STALWART (which stands for "Study of Aldesleukin with and Without Antiretroviral Therapy"). The study was comparing the effects of providing no treatment with the effects of intermittent cycles of IL-2 alone or IL-2 plus antiretrovirals in participants with early-stage HIV infection who do not yet meet the criteria to begin antiretroviral treatment. STALWART began in November 2005, and routine follow-up of the participants will continue until the end of February as originally planned.

Proleukin is approved by the U.S. Food and Drug Administration to treat adults with metastatic melanoma or metastatic kidney cell carcinoma. As a cancer treatment in the United States, it is administered to hospitalized patients for a shorter duration and at a higher dosage than those used in

the ESPRIT and SILCAAT clinical trials.

Source: NIH/National Institute of Allergy and Infectious Diseases